

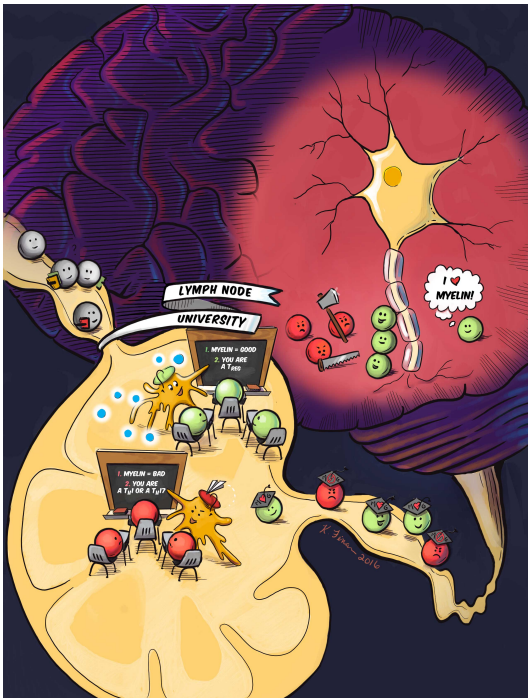


Lisa Tostanoski

University of Maryland (College Park, Md.)

\$15,000 Lemelson-MIT “Cure it!” Graduate Winner

Innovative Biomaterials-based Strategies to Combat Autoimmune Disease



Lymph node illustration by Kelly Finan

The Challenge: Autoimmune diseases arise when the body mistakes some part of itself for foreign tissue. Doctors treat autoimmune diseases, such as multiple sclerosis (MS), by generally suppressing the immune system. However, this approach doesn't cure disease and leaves patients vulnerable to infections. In MS, the immune system attacks myelin, the protective coating that insulates our neurons. Broad immunosuppression provides valuable relief from MS symptoms, but loses its effectiveness as the disease progresses and requires patients to receive life-long frequent treatments, such as daily injections or monthly infusions.

An idea being explored in the field is the potential to use vaccine-like therapies to treat autoimmunity. These strategies aim to specifically control the attack of self-molecules, like myelin in MS, while leaving the rest of the immune system intact. When myelin-specific regulatory

T cells (T_{REGS}) encounter myelin, they secrete molecules that can destroy or inactivate the inflammatory cells that typically drive the disease. T_{REGS} are also long-lived cell populations, which could provide a means for a durable therapy. Recent studies have demonstrated that co-delivering myelin peptide with a regulatory drug or cytokine can skew T cells that recognize myelin towards T_{REGS} with the desired therapeutic properties. However, injecting these signals into muscles or veins affords little control over where they end up, limiting their effectiveness and bathing the whole body in strong immune signals. Thus, new strategies that enable control over the combinations and doses of therapies that reach particular tissues in the body are creating great excitement in the field and, ultimately, could be transformative in the treatment of autoimmune diseases.

The Solution: Lisa's graduate research has developed two technologies to control the delivery of regulatory immune cues *in vivo* and promote tolerance:

In the first approach, she uses a targeted injection technique to deliver signals directly to lymph nodes, the tissues that orchestrate and direct our immune responses. Lisa deposits degradable polymer carriers – loaded

with the desired cargos – right where they need to be. These particles slowly degrade in lymph nodes, releasing signals that reprogram the function of lymph nodes to produce helpful regulatory immune cells that then leave these sites and move to the brain and spinal cord to control disease. When Lisa injected a single dose of tolerogenic microparticles in the lymph nodes at the peak of MS-like disease, paralysis was reversed in mice. These effects were permanent for the duration of the studies. The project has also revealed new understanding of how intra-LN injection of the polymer particles allows control over the immune function in the node and throughout the body. In particular, these experiments showed that local delivery can have beneficial effects on non-treated tissues, including the spinal cord – the site of disease in MS – that underscores the therapeutic effect observed: a halt or reversal of disease in mice. Moving forward, the team aims to exploit the modular nature of this platform. By changing the immune cargos encapsulated in the carriers, the application to other diseases – including type 1 diabetes and transplantation – is actively being explored.

In a second project, Lisa self-assembles immune cues – myelin peptide and a regulatory nucleic acid – built up layer-by-layer with electrostatic attraction to form carrier-free microcapsules. This immune polyelectrolyte multilayer (iPEM) technology results in structures composed entirely of immune signals. This “all therapeutic - no container” approach mimics some of the attractive features of conventional biomaterials – co-delivery, for example – but in a simple, modular approach that eliminates all synthetic or carrier components. When these iPEMs were delivered in an early-therapeutic regimen in the MS model described above, 100% of mice were protected from the development of disease-induced paralysis. In collaboration with Dr. Walter Royal and researchers in his laboratory, Lisa began pilot studies to investigate how iPEMs interact with samples from human MS patients. These experiments revealed that iPEMs could restrain the inflammatory profile of cells from MS patient blood samples, supporting the investigation of the translational potential of this approach. Toward this goal, the project team has been awarded more than \$2 million to determine how best to exploit these technologies for MS, to expand the work to other disease, and to study signaling in samples isolated from a larger patient cohort.

Commercialization: MS afflicts 2.3 million people representing a \$14 billion worldwide treatment market. Existing therapies compromise immunity and require regular, life-long treatments. Lisa's inventions, and the ongoing work being conducted by this multi-disciplinary research team, could help reveal new knowledge about immune tolerance and contribute to the design of novel therapies toward the goals of improving patient quality of life and reducing costs to society. To date, she has contributed to five intellectual property filings that have received interest from several large pharmaceutical companies.